Hypnotics

Part I. Acid Amides as Hypnotics. I. Acylureas
Part II. Acid Amides as Hypnotics. II. Acetamides

A DISSERTATION

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Acid Amides as Hypnotics. I. Acylureas[1]

By F. F. Blicke and A. P. Centolella[2]

The introduction of an acyl group such as diethylbromoacetyl or allylisopropylacetyl into urea converts the latter into an excellent hypnotic. Publications which illustrate the manner in which hypnotic activity varies with the nature of the acyl group are very few in number.

Table I

Substituted Malonic Esters, Malonic Acids, Acetic Acids and Acetyl Chlorides

		Malonic ester B. p., °C.	Mm.	Malonic acid[a] M. p., °C.	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	Acetic acid B. p., °C.	Mm.	Acetyl chloride B. p., °C.	Mm.
1	Propyl-β-phenylethyl	190–195	14	123–124	$C_{14}H_{18}O_4$	67.16	66.97	7.25	7.32	195–200	20	164–169	19
2	Isopropyl-β-phenylethyl	204–206	24	129–130	$C_{14}H_{18}O_4$	67.16	66.90	7.25	7.33	198–204	35	160–165	21
3	Allyl-β-phenylethyl	205–208	20	128–129	$C_{14}H_{16}O_4$	67.71	67.44	6.50	6.55	196–199	22	205–210	15
4	Isobutyl-β-phenylethyl	205–208	20	136–137	$C_{15}H_{20}O_4$	68.14	68.16	7.46	7.27	200–203	20	216–222	18
5	β-Cyclohexylethyl-β′-phenylethyl	255–260	30	134–135	$C_{19}H_{26}O_4$	71.64	71.36	8.24	8.24	245–250	19	220–225	25
6	Ethyl-γ-phenylpropyl	195–200	18	148–149	$C_{14}H_{18}O_4$	67.16	67.25	7.25	7.14	193–196	18	217–220	30
7	Ethyl-δ-phenylbutyl	216–220	22	114–115	$C_{15}H_{20}O_4$	68.14	68.33	7.46	7.57	227–230	50	190–194	22
8	Ethyl-ε-phenylamyl	230–235	25	106–107	$C_{16}H_{22}O_4$	69.02	69.23	7.97	7.98	213–219	20	199–204	20
9	Ethyl-ζ-phenylhexyl	227–233	18	67–68	$C_{17}H_{24}O_4$	69.83	69.56	8.28	8.19	218–222	17	206–210	21
10	Ethylcinnamyl	215–220	30	133–134	$C_{14}H_{16}O_4$	67.71	67.77	6.50	6.38	215–220	35	184–190	20

[a] The malonic acids were recrystallized from benzene.

Table II

Substituted Acetylureas

	Acetylurea[a]	M. p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
1	N-Methyl-diethyl	93–95	$C_6H_{16}O_2N_2$	16.26	16.06
2	Ethyl-propyl	200–201	$C_6H_{16}O_2N_2$	16.26	16.19
3	N-Methyl-ethyl-butyl	77–78	$C_{10}H_{20}O_2N_2$	13.98	13.78
4	Ethyl-butyl-α-bromo	84–85	$C_9H_{17}O_2N_2Br$	(30.10	30.17 Br)
5	Ethyl-amyl	138–139	$C_{10}H_{20}O_2N_2$	13.98	13.91
6	Ethyl-hexyl	126–127	$C_{11}H_{22}O_2N_2$	13.06	12.70
7	Ethyl-β-cyclohexylethyl	176–177	$C_{12}H_{24}O_2N_2$	11.66	11.71
8	Di-β-cyclohexylethyl	175–176	$C_{19}H_{34}O_2N_2$	8.68	8.77
9	β-Phenylethyl	174–175	$C_{11}H_{14}O_2N_2$	13.59	13.86
10	Ethyl-benzyl	141–142	$C_{12}H_{16}O_2N_2$	12.72	13.01
11	Ethyl-β-phenylethyl	152–153	$C_{13}H_{18}O_2N_2$	11.96	11.77
12	Di-β-phenylethyl	149–150	$C_{19}H_{22}O_2N_2$	9.15	9.25
13	Propyl-β-phenylethyl	148–150	$C_{14}H_{20}O_2N_2$	11.28	11.20
14	Isopropyl-β-phenylethyl	157–158	$C_{14}H_{20}O_2N_2$	11.28	11.47
15	Allyl-β-phenylethyl	115–116	$C_{14}H_{18}O_2N_2$	11.38	11.48
16	Butyl-β-phenylethyl	117–118	$C_{15}H_{22}O_2N_2$	10.68	10.70
17	Isobutyl-β-phenylethyl	149–150	$C_{15}H_{25}O_2N_2$	10.68	10.75
18	β-Cyclohexylethyl-β′-phenylethyl	148–149	$C_{19}H_{28}O_2N_2$	8.85	8.89
19	Ethyl-γ-phenylpropyl	143–145	$C_{14}H_{20}O_2N_2$	11.28	11.68
20	Ethyl-δ-phenylbutyl	137–138	$C_{15}H_{22}O_2N_2$	10.68	10.83
21	Ethyl-ε-phenylamyl	120–121	$C_{16}H_{24}O_2N_2$	10.10	10.35
22	Ethyl-ζ-phenylhexyl	122–123	$C_{17}H_{26}O_2N_2$	9.65	9.89
23	Ethylcinnamyl	139–140	$C_{14}H_{18}O_2N_2$	11.38	11.37

[a] The compounds were recrystallized in the following manner: compounds 8, 14, 18, 20, 21 and 22 from petroleum ether (90–100°); compound 7 from alcohol; compounds 3, 4, 11 and 16 from dilute alcohol; compounds 2, 5, 6, 9 and 12 from acetone; compound 13 from 50% acetone; compounds 10, 17 and 19 from a mixture of one part acetone and two parts petroleum ether; compounds 15 and 23 from a mixture of one part acetone and nine parts petroleum ether.

In this paper we have described a number of disubstituted acetylureas, $R_2CH\text{-}CO\text{-}NH\text{-}CO\text{-}NH_2$ (Table II), which were examined pharmacologically by Mr. J. W. Nelson and Dr. G. F.

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by A. P. Centolella in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) The Upjohn Company Fellow.

Cartland in The Upjohn Company Laboratories.[3] It was quite surprising to find that none of these ureas were effective to any great degree when injected intraperitoneally into white rats although, in a second paper, it will be shown that some of the corresponding acetamides are strong hypnotics.

The ureas were obtained by the following general method: conversion of malonic ester into the required disubstituted derivative, $R_2C(CO-OC_2H_5)_2$, hydrolysis of the ester, elimination of carbon dioxide with the formation of a disubstituted acetic acid, $R_2CH—COOH$, preparation of the corresponding acetyl chloride and treatment of the latter with urea or methylurea.[4]

The new intermediates are described in Table I.

Experimental Part

The procedures are illustrated in the case of allyl-β-phenylethylacetylurea.

To sodium ethylate, prepared from 1000 cc. of absolute alcohol and 46 g. of sodium, there was added, slowly, 320 g. of malonic ester. After one hour the mixture was stirred and refluxed and 370 g. of β-phenylethyl bromide added during the course of two hours. The mixture was stirred and refluxed for two hours longer, most of the alcohol removed by distillation and 500 cc. of water added to the cold residue. The ester layer was separated and the aqueous layer extracted six times with 75-cc. portions of ether; yield of β-phenylethylmalonic ester 424 g. or 80% of the calcd. amount; b. p. 182–185° (12 mm.).[5]

In a manner similar to that described above, allyl-β-phenylethylmalonic ester was prepared from sodium ethylate, obtained from 300 cc. of alcohol and 13.8 g. of sodium, 159 g. of β-phenylethylmalonic ester and 73.2 g. of allyl bromide; yield 159 g. or 88% of the calcd. amount.

A mixture of 80 g. of potassium hydroxide, 250 cc. of 70% alcohol and 101 g. of the disubstituted malonic ester was refluxed for twenty-four hours, most of the alcohol removed, 250 cc. of water added and then about 140 cc. of hydrochloric acid added to the cold mixture. The crude acid separated from the acidic mixture as an oil but soon solidified; yield 78 g. or 94% of the calcd. amount.

Fifteen grams of the allyl-β-phenylethylmalonic acid was heated in an oil-bath at 180° until most of the carbon dioxide had been evolved and then heated at 150–160° for six hours; yield 10.7 g. or 86% of the calcd. amount.

A mixture of 28 g. of the acetic acid and 45 g. of commercial thionyl chloride was heated for two hours on a steam-bath after the initial vigorous reaction had subsided and the excess thionyl chloride then removed; the yield of acid chloride was 21 g. or 70% of the calcd. amount.

Nine grams of allyl-β-phenylethylacetyl chloride and 9.6 g. of dry urea were heated in an oil-bath at 125°. As soon as the material had melted the temperature was dropped to 110–115°. After six hours the product was cooled and rubbed in a mortar with enough 10% sodium carbonate solution to keep the mixture alkaline. The solid material was filtered, washed with water and recrystallized; yield 8.9 g. or 90% of the calcd. amount.

Summary

A number of new disubstituted malonic esters, malonic acids, acetic acids, acetyl chlorides and acetylureas have been described.

No strong hypnotics were found among the disubstituted acetylureas, $R_2CH—CO—NH—CO—NH_2$, studied.

ANN ARBOR, MICHIGAN RECEIVED OCTOBER 10, 1938

(3) Their results will be published by them in detail in another journal.

(4) Davis and Blanchard, THIS JOURNAL, **51**, 1797 (1929).

(5) Dolique [*Ann. chim.*, [10] **15**, 447 (1931)] reported 184–185° at 15 mm.

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[Contribution from the College of Pharmacy, University of Michigan]

Acid Amides as Hypnotics. II. Acetamides[1]

By F. F. Blicke and A. P. Centolella[2]

It has been known for a long time that certain representatives of three types of acid amides—substituted acetamides, acylureas and cyclic amides such as substituted barbituric acids and hydantoins—exhibit strong hypnotic activity.

During late years, due to the popularity of barbituric acid compounds, the study of the acetamide type has been neglected except for the publications of Volwiler and Tabern[3] and of Junkmann.[4]

Most of the acetamides, described hitherto as compounds which possess hypnotic action, are trisubstituted derivatives such as diethylallylacetamide. Since, in general, trisubstituted acetamides are more difficult to obtain than the disubstituted compounds we have prepared a considerable number of the latter in order to determine their activity as hypnotics.

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by A. P. Centolella in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) The Upjohn Company Fellow.

(3) Volwiler and Tabern, This Journal, **58**, 1353 (1936).

(4) Junkmann, *Arch. expll. Path. Pharmakol.*, **186**, 552 (1937).

TABLE I

SUBSTITUTED ACETAMIDES

The amides were recrystallized in the following manner: compound 4 was recrystallized from water; compounds 2, 5, 9, 10, 14, 16, 17, 18, 21 and 25 from petroleum ether (90–100°); compounds 6, 11, 12 and 20 from dilute alcohol; compounds 13, 15 and 22 from 50% acetone and compound 19 from acetone.

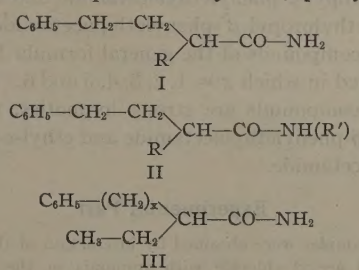
	Acetamide	M. p., °C.	Formula	Nitrogen, % Calcd.	Found
1	Diethylthio	80–81	$C_6H_{13}NS$	(24.45	24.50 S)
2	N-Methyldiethyl	79–80	$C_7H_{15}ON$	10.84	10.76
3	N-Butyldiethyl	34–35	$C_{10}H_{21}ON$	8.15	8.00
4	Ethylbutyl	106–107[a]	.....	..	..
5	N-Methylethylbutyl	69–70	$C_9H_{19}ON$	8.93	9.07
6	N-Ethylethylbutyl	58–59	$C_{10}H_{21}ON$	8.18	7.94
7	N-β-Hydroxyethylethylbutyl	47–49[b]	$C_{10}H_{21}O_2N$	7.48	7.25
8	N-Butylethylbutyl	Oil[c]	$C_{12}H_{25}ON$	7.03	6.77
9	Ethylamyl	102–103[d]	$C_9H_{19}ON$	8.99	8.91
10	Ethylhexyl	106–107	$C_{10}H_{21}ON$	8.18	8.06
11	Ethyl-β-cyclohexylethyl	134–135	$C_{12}H_{23}ON$	7.10	7.09
12	N-Methylethyl-β-cyclohexylethyl	111–112	$C_{13}H_{25}ON$	6.63	6.65
13	N-Ethylethyl-β-cyclohexylethyl	96–97	$C_{14}H_{27}ON$	6.21	6.07
14	N-β-Hydroxyethylethyl-β′-cyclohexylethyl	90–91	$C_{14}H_{27}O_2N$	5.82	5.80
15	N-Butylethyl-β-cyclohexylethyl	61–62	$C_{16}H_{31}ON$	5.53	5.39
16	Di-β-cyclohexylethyl	173–174	$C_{18}H_{33}ON$	5.01	5.07
17	N-Methyldi-β-cyclohexylethyl	164–165	$C_{19}H_{35}ON$	4.78	4.80
18	N-Ethyldi-β-cyclohexylethyl	137–138	$C_{20}H_{37}ON$	4.56	4.78
19	Butyl-β-cyclohexylethyl	140–141	$C_{14}H_{27}ON$	6.21	6.26
20	N-Methylbutyl-β-cyclohexylethyl	110–111	$C_{15}H_{29}ON$	5.85	5.55
21	N-Ethylbutyl-β-cyclohexylethyl	94–95	$C_{16}H_{31}ON$	5.53	5.64
22	N-β-Hydroxyethylbutyl-β′-cyclohexylethyl	92–93	$C_{16}H_{31}O_2N$	5.20	5.13
23	N-(Diethylacetyl)-morpholine	Oil[e]	$C_{10}H_{19}O_2N$	7.56	7.21
24	N-(Ethylbutylacetyl)-morpholine	Oil[f]	$C_{12}H_{23}O_2N$	6.57	6.32
25	N,N′-*bis*-(Diethylacetyl)-ethylenediamine	230–231	$C_{14}H_{26}O_2N_2$	10.95	10.70

[a] Raper [*J. Chem. Soc.*, **91**, 1837 (1907)] reported 101–102°. [b] B. p. 199–200° at 15 mm. [c] B. p. 177–178° at 5 mm. [d] Volwiler and Tabern [THIS JOURNAL, **58**, 1353 (1936)] found 96°. [e] B. p. 159–160° at 9 mm. [f] B. p. 185–186° at 9 mm.

In Table I of this paper there have been described di-*n*-alkyl- and *n*-alkyl-β-cyclohexylethylacetamides and, in some instances, corresponding N-alkyl and N-hydroxyalkyl derivatives. The evaluation of all of our compounds, from the pharmacological standpoint, has been carried out by Mr. J. W. Nelson and Dr. G. F. Cartland in The Upjohn Company Laboratories and the data obtained will be published by them in another journal. However, it may be stated that the following amides in Table I have been shown to be very effective hypnotics when injected intraperitoneally into white rats: diethylthio-, ethylbutyl-, N-methylethylbutyl-, ethylamyl-, ethylhexyl- and N-β-hydroxyethylethyl-β′-cyclohexylethylacetamide.

Especially interesting is the relatively high activity of diethylthioacetamide; in fact, it is the strongest hypnotic in the group (Table I) and is approximately five times as potent as diethylacetamide. However, the therapeutic index (minimum lethal dose/minimum hypnotic dose) of both diethylthioacetamide and diethylacetamide is low, 1.2 in each instance.

The disubstituted acetamides, described in Table II, are of three types. In type I, one substituent is represented by the β-phenylethyl



group, the other, R, by ethyl, propyl, isopropyl, allyl, butyl, isobutyl, β-cyclohexylethyl or β-phenylethyl. In this group the ethyl, propyl, isopropyl, allyl and isobutyl compounds are strong hypnotics.

A second type, II, represents compounds of type I in which a substituent, R′, has been in-

TABLE II

SUBSTITUTED ACETAMIDES

The amides were recrystallized in the following manner: compound 2 from water; compounds 8, 9, 10, 11, 12, 15, 16, 20, 22, 24, 25, 26 and 27 from petroleum ether (90–100°); compounds 18, 19 and 21 from dilute alcohol; compound 17 from acetone; compound 13 from 50% acetone; compounds 5 and 23 from a mixture of one part acetone and two parts petroleum ether (90–100°); compounds 1, 4, 6, 7, 10 and 14 from a mixture of one part acetone and nine parts petroleum ether.

	Acetamide	M. p., °C.	Formula	Nitrogen, % Calcd.	Found
1	Ethylbenzyl	117–118	$C_{11}H_{15}ON$	7.90	8.00
2	Ethyl-β-phenylethyl	105–106[a]	$C_{12}H_{17}ON$	7.32	7.30
3	N-Methylethyl-β-phenylethyl	98–99	$C_{13}H_{19}ON$	6.83	6.93
4	N-Ethylethyl-β-phenylethyl	72–73	$C_{14}H_{21}ON$	6.39	6.56
5	Di-β-phenylethyl	162–163	$C_{18}H_{21}ON$	5.53	5.42
6	N-Methyldi-β-phenylethyl	124–125	$C_{19}H_{23}ON$	5.24	5.15
7	N-Butyldi-β-phenylethyl	86–87	$C_{22}H_{29}ON$	4.43	4.29
8	β-Cyclohexylethyl-β′-phenylethyl	170–171	$C_{18}H_{27}ON$	5.14	5.41
9	Propyl-β-phenylethyl	109–110	$C_{13}H_{19}ON$	6.81	6.78
10	N-Methylpropyl-β-phenylethyl	93–94	$C_{14}H_{21}ON$	6.39	6.33
11	N-Ethylpropyl-β-phenylethyl	84–85	$C_{15}H_{23}ON$	6.00	6.08
12	N-β-Hydroxyethylpropyl-β′-phenylethyl	74–75	$C_{15}H_{23}O_2N$	5.63	5.70
13	N-Butylpropyl-β-phenylethyl	69–70	$C_{17}H_{27}ON$	5.36	5.23
14	Isopropyl-β-phenylethyl	121–122	$C_{13}H_{19}ON$	6.81	6.85
15	N-β-Hydroxyethylisopropyl-β′-phenylethyl	83–84	$C_{15}H_{23}O_2N$	5.63	5.55
16	Allyl-β-phenylethyl	90–91	$C_{13}H_{17}ON$	6.89	7.13
17	Butyl-β-phenylethyl	124–125	$C_{14}H_{21}ON$	6.40	6.56
18	N-Methylbutyl-β-phenylethyl	108–109	$C_{15}H_{23}ON$	6.00	5.75
19	N-Ethylbutyl-β-phenylethyl	71–72	$C_{16}H_{25}ON$	5.67	5.85
20	N-β-Hydroxyethylbutyl-β′-phenylethyl	66–67	$C_{16}H_{25}O_2N$	5.36	5.25
21	N-Butylbutyl-β-phenylethyl	59–60	$C_{18}H_{29}ON$	5.28	5.01
22	Isobutyl-β-phenylethyl	89–90	$C_{14}H_{21}ON$	6.40	6.61
23	Ethyl-γ-phenylpropyl	118–119	$C_{13}H_{19}ON$	6.81	6.82
24	Ethyl-δ-phenylbutyl	107–108	$C_{14}N_{21}ON$	6.40	6.43
25	Ethyl-ε-phenylamyl	98–99	$C_{15}H_{23}ON$	6.01	6.12
26	Ethyl-ζ-phenylhexyl	113–114	$C_{16}H_{25}ON$	5.67	5.75
27	Ethylcinnamyl	94–96	$C_{13}H_{17}ON$	6.89	6.72

[a] Levy [*Compt. rend.*, **194**, 175 (1932)] found 104° but did not record an analysis.

troduced into the amide group; R′ = methyl, ethyl, butyl or β-hydroxyethyl. Three compounds in this series proved to be strong hypnotics: N-ethylethyl-β-phenylethylacetamide, N-ethylpropyl-β-phenylethylacetamide and N-β-hydroxyethylpropyl-β′-phenylethylacetamide.

Six compounds of the general formula III were prepared in which $x = 1, 2, 3, 4, 5$ and 6. Two of these compounds are strong hypnotics, namely, ethyl-β-phenylethylacetamide and ethyl-ε-phenylamylacetamide.

Experimental Part

The amides were obtained by interaction of the disubstituted acetyl chloride with ammonia or the required amine. The new acid chlorides and their general method of preparation were described previously.[5]

Allyl-β-phenylethylacetamide was obtained in 87% yield when 4.5 g. of allyl-β-phenylethylacetyl chloride was added slowly, with vigorous stirring, to 20 cc. of ammonia water which was cooled with ice.

To prepare N,N′-bis-(diethylacetyl)-ethylenediamine 20 cc. of a 66% aqueous solution of ethylenediamine was stirred, cooled and 2.6 g. of diethylacetyl chloride added dropwise. The precipitate was filtered, washed with water, dried and recrystallized four times from petroleum ether; yield 2.4 g. or 95% of the calcd. amount.

No attempt was made to discover a satisfactory procedure for the preparation of diethylthioacetamide. However, sufficient material for our purpose was obtained when 22 g. of phosphorus pentasulfide and 23 g. of diethylacetamide were mixed intimately, 175 cc. of benzene added and the mixture refluxed for five minutes. The warm benzene was decanted from the pasty residue and the latter extracted with three 25-cc. portions of hot benzene. The solvent was removed from the combined benzene solutions and the gummy, yellow residue recrystallized from petroleum ether (90–100°).

Summary

A number of new dialkyl-, alkyl-β-cyclohexylethyl- and alkyl-β-phenylethylacetamides have been described. In some instances N-alkyl derivatives were prepared.

Some of the amides have been found to be strong hypnotics.

(5) Blicke and Centolella, THIS JOURNAL, **60**, 2923 (1938).

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